Receptors and Second Messengers

Introduction

This is the physiology lesson on receptors with a lot of the same information you encountered in General Physiology. If you've already done Gen Phys, you'll find the information contained within redundant. If you haven't done it recently, or not at all, be sure to pay attention in this lesson. The reason we have you engage this material again is so that it becomes second nature. As we progress into lessons 8, 9, and 10 about the autonomic nervous system, you will need to be able to see "M_3 via G_q" and know intuitively that G_q is a metabotropic receptor that involves calcium and therefore dilation or contraction of smooth muscles, whereas "nAChR is ionotropic" means Na^+ and K^+ both flow, altering membrane potentials. Getting hung up on "what does G_q mean again?" or "which ions in that ionotropic receptor?" once we get into the autonomic lessons will make learning that content daunting. We include receptor tyrosine kinases and steroid receptors for completeness.

General Physiology had a lot of details on how these receptors work. What we want you focused on here is not how they work (GTP-bound trimers) but associating what the downstream targets are. The goal here is to learn to equate a **receptor type** with an **intracellular messenger system** (the word "system" should imply, "learn the whole pathway," not just one messenger).

If you haven't done the lesson on receptors from General Physiology and you start to get lost, it might be worth doing that one first. We go fast in this lesson.

Vocabulary

Ligands activate receptors. Ligands can be anything, but fall into two main categories: hydrophilic and lipophilic. Ligands can be drugs we administer or they can be endogenous compounds made by our bodies. Ligands bind to and activate receptors. **Receptors** are the things ligands bind to that initiate intracellular signals of various kinds. Receptors can be in the cell membrane (which bind to hydrophilic ligands) or in the cytoplasm (which bind to lipophilic ligands).

Hydrophilic (water-soluble) ligands bind to transmembrane receptors in the target cell's plasma membrane. These ligands can't cross the membrane because they're lipophobic. The signal initiated by the extracellular portion of their receptor must be translated across the membrane to the cytoplasmic side. This requires the receptor protein to **span the membrane** from the extracellular matrix to the cytoplasm, where it transmits the signal to an **intracellular second messenger**. The second messenger can also be used to propagate the system—one ligand binds on the cell membrane, 20 intracellular messengers are dispatched in the cytoplasm.

Ligand-binding can result in any number of effects. The **opening of ion channels** changes the voltage of the cell, and the effect is **immediate** (called ionotropic). On the other extreme, those drugs that activate **transcription factors** influence **gene expression**, and will take a **long time to have an effect**. This type of receptor effect is often longest-lasting of any receptor effects, and could even alter the cell entirely, but gene expression takes time. In between these two is **intracellular dephosphorylation**—the target of which could be anything: another protein, a voltage channel, a transcription factor, etc. The complexity and interplay are infinite, so we're going to look at each system in a vacuum, and end with the second-messenger effect. That's also how you'll be tested if they get down and dirty like this—when a receptor is activated, it does one of three things: a channel opens, downstream targets are phosphorylated, or gene transcription is altered.

Lipophilic (lipid-soluble) ligands can readily pass through membranes of cells and bind their receptors in the cytoplasm. These are **steroids**. They most often have the effect of altering gene expression by going to the nucleus and binding with DNA.

System #1: Cell-Membrane Receptor, G Protein-Coupled, G_s/G_i-cAMP-PKA-Phosphorylation

The **ligand** is **hydrophilic**, so the **receptor** is within the **cell membrane** (the receptor consisting of seven transmembrane domains) that allows the receptor to translate the message from the extracellular space to the cytoplasm. The cytoplasmic side of this receptor interacts with a **G protein** to initiate the intracellular cascade.

This system is actually two systems in one. Two different receptors (one **stimulatory**, one **inhibitory**) bind two different ligands that act through two different **G proteins** (one **stimulatory**, one **inhibitory**), merging at one common point. One ligand binds to one receptor that activated G_s, and stimulates the system. Another ligand binds to another receptor that activates G_i, and inhibits the system. They are taught together because the entire rest of the two pathways are identical.

The target of the G-coupled protein is adenylyl cyclase (**AC**). G_i inhibits AC; G_s stimulates AC. Adenylyl cyclase does one thing: converts ATP to **cAMP**. cAMP activates protein kinase A (**PKA**), which in turn **phosphorylates something**. The something it phosphorylates has a change in function. Phosphorylation does NOT mean "turns on" or "turns off." It means "changes function from state." It could mean on, it could mean off. The effect could go to a membrane ion channel, it could go to the nucleus, it could go to any downstream target. What's critical to memorize is G protein-AC-cAMP-PKA-phosphorylation.

CREB (cAMP response element-binding protein) is a cellular transcription factor. Once phosphorylated, it binds to certain DNA sequences called cAMP response elements (CRE). It is one possible target of PKA.

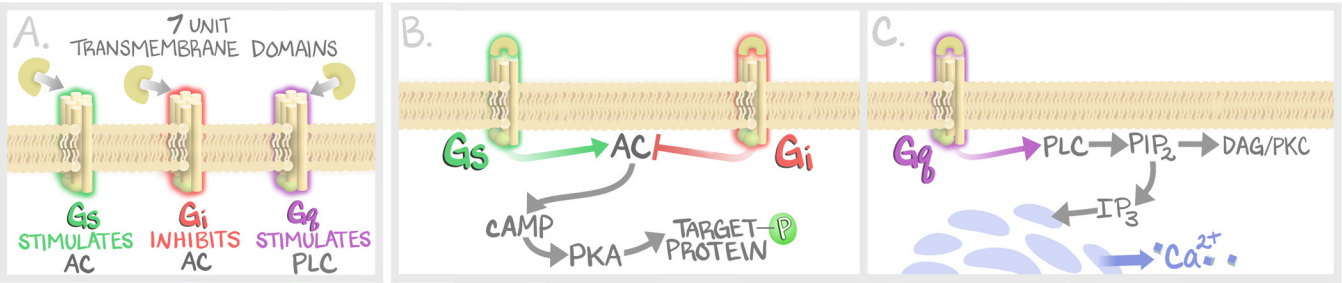

Figure 7.1: G Protein-Associated Systems
(a) Transmembrane receptors bind their ligand on the extracellular side, then activate a GTP-associated protein on the cytoplasmic side. (b) The adenylyl cyclase-cAMP-PKA pathway starts with G_s, which stimulates the system, or G_i, which inhibits the system. (c) The G_q pathway involves phospholipase C and cleavage of PIP_2 into membrane-attached DAG and cytoplasmically active IP_3, which releases calcium from the sarcoplasmic reticulum, leading to smooth-muscle contraction.

System #2: G_q IP_3/DAG/Ca

The **ligand** is **hydrophilic**, so the **receptor** is within the **cell membrane** as a 7-transmembrane domain that allows the receptor to translate the message from the extracellular space to the cytoplasm. The cytoplasmic side of this receptor interacts with a **G protein** to initiate the intracellular cascade. But that G protein is not the G_s or G_i associated with the AC-cAMP-PKA pathway. This is a different G protein, and a different messenger system.

The G protein in this case is $\mathbf{G_q}$ and has a very different intracellular target. G_q activates **phospholipase C**, which acts on an intramembrane substrate called $\mathbf{PIP_2}$. PIP_2 gets cleaved, its hydrophobic end **DAG** remaining in the membrane, while its hydrophilic end $\mathbf{IP_3}$ goes to the cytoplasm. $\mathbf{IP_3}$ deploys **calcium** from the **sarcoplasmic reticulum**. Calcium is then used for contraction. This is almost **always smooth muscle**.

At the same time, the **calcium released + DAG + PKC** (protein kinase C) serves as the feedback loop to turn off calcium influx. DO NOT ENGAGE the mechanism of PKC. Just know that PKA is for G_S-cAMP-PKA (A for cAMP) and PKC is for G_q-PLC-Ca-PKC.

This system, which focuses on calcium influx into the cytoplasm, is often found in smooth-muscle contraction cells. Activation of this system leads to calcium release, resulting in smooth-muscle contraction. The organ in which the smooth muscle is contracting will determine the ultimate effect—bronchioles, vasculature, intestines, etc.

System #3: Transport Proteins That Are Ion Channels: Ionotropic

Sometimes all that happens is that a channel opens. If the channel is for ions, it alters charge. Sometimes it lets in a substrate. When the ligand is **unbound**, the **conformation is unfavorable** for the passage of the substrate. Then, upon binding the ligand, there's a **conformation change** in the transport protein that allows passage.

An example of this is the nicotinic receptors of preganglionic neurons in the autonomic nervous system. Binding of the acetylcholine neurotransmitter to the nicotinic-acetylcholine receptor induces a conformational change that allows sodium into the cell and potassium out. More details in #8: *Intro to Autonomics*.

System #4: Tyrosine Kinase Receptors (aka JAK/STAT)

We are going to discuss one such receptor system, the JAK/STAT pathway. It's a cell-membrane receptor that binds a hydrophilic ligand. It starts as monomers within the cell membrane, inactive. When a ligand binds, the receptor **dimerizes**. Upon dimerization, the two dimers **autophosphorylate each other**. Once they do, they then **phosphorylate** certain intracellular targets. The JAK receptor phosphorylates itself, then phosphorylates STAT. STAT then has downstream effects. This is best known as the growth factor receptor that produces CML. JAK is the receptor, STAT is the intracellular pathway. Other catalytic receptors exist (the generic name for this class of receptor), and the downstream effect can be phosphorylation or dephosphorylation. This is included for completeness, as this type of receptor will not be part of the autonomic discussion that follows in Pharmacology.

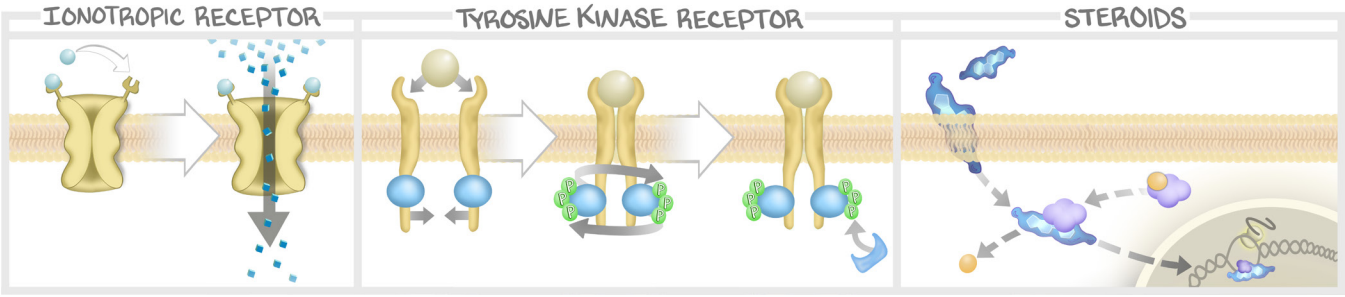

Figure 7.2: Other Receptor Systems
Ionotropic receptors are gated pores that open when activated, allowing ions to flow. Catalytic receptors such as tyrosine kinase receptors bind ligands as monomers, dimerize and autophosphorylate, then take their effect on second messengers in the cytoplasm. Steroid receptors bind lipophilic ligands, then translocate to the nucleus to effect gene expression.

System #5: Steroid Receptors

This system's ligands are **lipophilic**, so they freely pass through cell membranes. These ligands have **intracellular receptors**. Binding of a steroid ligand to its receptor almost always results in **translocation to the nucleus**. It binds the **hormone response element** on DNA and alters **gene expression**. Like catalytic receptors, this is included for completeness and is not part of the autonomic discussion that follows.